REMARKS

Status

Upon entry of the amendments above, Claims 1-12 are pending, with Claims 1-12 under active consideration. The claims have been amended to merely clarify some language and the amendments are editorial in nature.

Accordingly, this Amendment incorporates no new matter.

Claim Rejections - 35 U.S.C. § 103

The Office Action rejects Claims 1-3, 5-7, and 9-12 under 35 U.S.C. § 103(a) as unpatentable based on Majeed et al., U.S. Patent No. 6,436,991, alone.

The Office Action rejects Claim 4 under 35 U.S.C. § 103(a) as unpatentable based on Majeed et al. combined with Remington's (1995).

The Office Action rejects Claim 8 under 35 U.S.C. § 103(a) as unpatentable based on Majeed et al. combined with Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 9th Edition (1995).

Applicants respectfully traverse.

The prior art fails to teach or suggest a method of treating a cognitive memory dysfunction in a mammal, said method comprising administering to the mammal a pharmaceutically acceptable composition consisting essentially of a memory enhancing effective amount of *gugulipid,* wherein said *gugulipid* is prepared by a method comprising extracting a resin from the aerial branches of the plant *C. wighitii* and said resin is extracted by a process comprising: a) suspending a gum or resin of the plant in a non-polar solvent; b) filtering or decanting the soluble portion; c) extracting a fatty acid; d) extracting the residue with ethyl acetate using shaking or sonication; e) mixing the polar and non-polar fractions; f) filtering to remove the solid suspension; and g) removing the solvent to obtain the *gugulipid.*

Applicants particularly note that the Office Action incorrectly asserts that 1) the ferulate compounds disclosed in Majeed et al. teach or suggest the *gugulipid* extract designated in the claims; and 2) that the suggested treatment of Alzheimer's disease in Majeed et al. teaches or suggests a method of treating a cognitive memory dysfunction as claimed. On both these points, the Office Action is erroneous. Thus, since all the claim-designated elements of the invention have not been adequately addressed, no *prima facie* case of obviousness has been made out.

Furthermore, the assertion in the Office Action that the burden of proof has been shifted to the Applicants is also erroneous. It is premature for the Examiner to require some showing of non-obviousness when no *prima facie* case of obviousness has first been established. Nevertheless, Applicants respectfully note that the data in Applicants' specification with respect to overcoming cognitive memory dysfunction using *gugulipid* extract would rebut any *prima facie* case of obviousness.

First, the Office Action is mistaken that Majeed et al. discloses ferulate compounds that meets the claim-designated *gugulipid* extract. This mistake appears to be premised on that because the ferulate compounds in Majeed et al. are isolated from parts of the plant *C. wighitii*, they are also necessarily present in the claim-designated *gugulipid* extract. This premise is without adequate basis in that there is no assurance whatsoever that the ferulate compounds in Majeed et al. are even present in the claim-designated *gugulipid* extract. The ferulate compounds in Majeed et al. are obtained in a very different way than the claim-designated *gugulipid* extract. As such, these ferulate compounds may not even be present in the claim-designated *gugulipid* extract.

However, even assuming *in arguendo* that these ferulate compounds disclosed in Majeed et al. were present in any significant quantity in the claim-designated *gugulipid* extract, this alone is still totally insufficient to teach or suggest the claim-designated *gugulipid* extract in the method

claimed because the extract will assuredly contain additional components, beyond simply the ferulate compounds. Furthermore, because the ferulate compounds in Majeed et al. are isolated in themselves, they are separated from additional components such as are preserved in the extraction process steps delineated in Applicants' claims.

The assertion in the Office Action that this argument would not be persuasive "since there are no advantageous properties shown or described in the particular method steps used to obtain the guggulipid ingredient." The burden is upon the Examiner to show that either the extract is disclosed in the prior art, or to show that the ferulate compounds are present in the extract coupled with a showing how the remaining components are inconsequential. This the Examiner has not done.

Furthermore, the Office Action repeatedly refers to the disclosure of treating Alzheimer's disease that is tangentially mentioned in Majeed et al. with respect to the ferulate compounds disclosed there. Applicants respectfully point out this disclosure in Majeed et al. with respect to Alzheimer's disease does not address all cognitive memory dysfunction outside of Alzheimer's disease, but more importantly, the disclosure would be insufficient to motivate one of ordinary skill in the art to practice a method of treating Alzheimer's disease even with the ferulate compounds disclosed in Majeed et al. This is so because one of ordinary skill in the art, having the knowledge of one of ordinary skill in the art of a medical physician trained in treating neurodegenerative disorders, upon reading Majeed et al., would recognize the teaching there as rank speculation. In Majeed et al, at column 4, line 40-45, it is merely postulated that other properties of the disclosed ferulates might also "...provide a valid strategy in the treatment of neurodegenerative diseases..." As is well-known in the art, development of methods of treating Alzheimer's disease is notoriously unpredictable since the actual mechanisms of the disease are not fully known. See, for instance, Boron et al., Neurology (1997 May) 48 (5 Suppl 6): S17-24.

See particularly, page S23, the "Comment" in column 1.

There is absolutely no data in Majeed et al., either disclosed or incorporated, that would in any way adequately support this proposition. The disclosure there is both without credibility and not enabling to guide one of ordinary skill in the art in the treatment of any neurodegenerative disease, much less Alzheimer's disease. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See also Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991); In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

By way of contrast, Applicants' specification at pages 9-12, discloses *in vivo* data demonstrating the memory cognitive advances associated with treatments involving the claim-designated *gugulipid* extract. This showing is with regard to the whole extract.

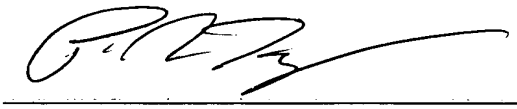
Accordingly, for all the reasons given above, the obviousness rejections are overcome. Reconsideration and withdrawal are respectfully requested.

CONCLUSION

All rejections having been addressed by the present response, Applicants assert that the present case is in condition for allowance and respectfully request early notice to that effect. If any issues remain to be addressed in this matter which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

PIPER RUDNICK LLP



Steven B. Kelber
Registration No. 30,073
Attorney of Record

Patrick R. Delaney
Registration No. 45,338

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085

In re Rinehart, 189 USPQ 143 (CCPA 1976)

In re Rinehart

(CCPA)
189 USPQ 143

Decided Mar. 11, 1976
No. 75-608
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Double patenting — Copending applications (§ 33.5)

Double patenting rejection that was based on copending parent application and affirmed by Board of Appeals is mooted by parent application's express abandonment after board's decision.

2. Patentability — Anticipation — Combining references (§ 51.205)

Patentability — Invention — In general (§ 51.501)

Determination under 35 U.S.C. 103 requires consideration of entirety of disclosure made by prior art references to those skilled in art.

3. Patentability — Invention — In general (§ 51.501)

Prima facie case of obviousness is established when teachings of prior art appear to suggest claimed subject matter to person of ordinary skill in art; it is incumbent upon applicant to go forward with objective evidence of unobviousness once prima facie case is established.

4. Board of Appeals — In general (§ 19.05)

Patentability — Invention — In general (§ 51.501)

Prior adjudication — New evidence or new issues (§ 56.25)

It was error to adopt earlier conclusion of prima facie obviousness that was based on parent application

and cited references when Board of Appeals had continuation application, prior art, and unrebutted facts established by inventor's affidavit before it, so that no question of prima facie obviousness remained; obviousness determination must be made in light of all evidence.

5. Patentability — Evidence of — In general

Patentability — Invention — In general (§ 51.501)

Patentability — Invention — Law or fact question (§ 51.507)

Concept of prima facie obviousness is not segmented concept; decision-maker must start over when rebuttal evidence is submitted after prima facie obviousness is established; question of whether applicant's burden of going forward to rebut prima facie case has been successfully carried requires that entire path to decision be retraced; earlier decision should not be considered as set in concrete and applicant's rebuttal evidence evaluated only on its knockdown ability; prima facie obviousness is legal conclusion, not fact; facts established by rebuttal evidence must be evaluated along with facts on which earlier conclusion was reached, not against conclusion itself.

6. Applications for patent — Continuing (§ 15.3)

Patentability — Change — Proportions (§ 51.259)

Mere inclusion of "commercial scale production" and "commercial scale quantities" in claims of continuation application does not patentably distinguish them over claims of parent application.

7. Patentability — Change — Proportions (§ 51.259)

Patentability — Invention — In general (§ 51.501)

Mere scaling up of prior art process capable of being scaled up would not establish patentability in claim to old process so scaled; mere use of commercial quantities cannot establish unobviousness of invention as whole.

8. Affidavits — Distinguishing from references (§ 12.7)

Patentability — Change — Proportions (§ 51.259)

Reference to "commercial scale quantities" in claims and inventor's affidavit establishes invention's environment, outlining problem solved and giving dimension to inventor's contribution, but does not establish patentability.

9. Patentability — Anticipation — Combining references (§ 51.205)

Patentability — Change — Proportions (§ 51.259)

Patentability — Invention — In general (§ 51.501)

Some predictability of success is required in any attempt to combine elements of reference processes in commercial scale operation; view that success would have been "inherent" cannot substitute for showing of reasonable expectation of success; inherency and obviousness are entirely different concepts.

10. Court of Customs and Patent Appeals — Issues determined — Ex parte patent cases (§ 28.203)

Patentability — Anticipation — Combining references (§ 51.205)

Patentability — Change — Proportions (§ 51.259)

Patentability — Invention — In general (§ 51.501)

Absence of suggestion in prior art patents that features of one should be combined with those of other to achieve commercial scale production of which neither is capable requires conclusion that obviousness rejection of claims directed to commercial scale production was improper, making it unnecessary for court to consider allegations of commercial success and satisfaction of long-felt need.

Particular patents — Resin

Rinehart, Process for Preparing Resin, rejection of claims 1-9 reversed.

Case History and Disposition:

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of VerneR. Rinehart, Serial No. 130,743, filed Apr. 2, 1971, continuation in part of application Serial No. 667,854, filed Sept. 14, 1967, continuation in part of application Serial No. 254,754, filed Jan. 29, 1963. From decision rejecting claims 1-9, applicant appeals. Reversed.

Attorneys:
Paul H. Heller, New York, N.Y. (Hugh A. Chapin, Kenyon & Kenyon Reilly Carr & Chapin, and MalvinR. Mandelbaum, all of New York, N.Y., and Ford W. Brunner and James M. Wallace, Jr., both of Akron, Ohio, of counsel) for appellant.

Joseph F. Nakamura (Jack E. Armore, of counsel) for Commissioner of Patents and Trademarks.

Judge:
Before Markey, Chief Judge, and Rich, Baldwin, Lane, and Miller, Associate

Opinion Text

Opinion By:
Markey, Chief Judge.

This is an appeal from the decision of the Patent and Trademark Office Board of Appeals (board) affirming the examiner's final rejection of claims 1 through 9, which are all the claims in appellant's (Rinehart's) application serial No. 130,743, filed April 2, 1971 [1] entitled "Process for Preparing Resin." We reverse.

The Invention

Commercial scale quantities of polymeric ethylene terephthalate (PET) are produced in either a batch or continuous process by heating a dicarboxylic acid with glycol in the presence of a preformed low molecular weight polyester solvent [2] under superatmospheric pressure and utilizing a low ratio of glycol to acid. The product may be conventionally condensation polymerized in the presence of a catalyst.

The claims have been treated together by Rinehart and the solicitor and will be so treated here. Claims 1 and 4 are illustrative:

> 1. The method for the commercial scale production of polyesters which com
>
> Page 145
>
> prises adding commercial scale quantities of ethylene glycol and a free aromatic dicarboxylic acid in the molar ratio of glycol to acid of from 1.7:1 to 1.05:1 to a solvent consisting of a preformed low molecular weight linear condensation polyester of a glycol and a dicarboxylic acid, said polyester having an average degree of polymerization of from 1.4 to 10, heating and reacting the mixture at a temperature above the melting temperature of the low molecular weight linear polyester at a pressure of from about 20 to about 1000 pounds per square inch gauge pressure until a linear condensation polyester resin of said glycol and acid having an average degree of polymerization of from 1.4 to 10 is formed.
>
> 4. The method for the commercial scale production of polyesters which comprises continuously adding commercial scale quantities of ethylene glycol and terephthalic acid in the ratio of from 1.7:1 to 1.05:1 of ethylene glycol to terephthalic acid to a solvent consisting of low molecular weight ethylene glycol-terephthalate polyester having an average degree of polymerization of from 1.4 to 10 while heating and reacting the mixture at a temperature above the melting temperature of the low molecular weight ethylene glycol-terephthalate polyester at a pressure range of from about 20 to about 1000 pounds per square inch gauge pressure, continuously venting the water vapor formed in the reaction at such a rate that the pressure in the system is maintained constant within said pressure range and continuously withdrawing an amount of low molecular weight ethylene glycolterephthalate polyester about equal to the amount of ethylene glycol and terephthalic acid added.

Board

[1] The board affirmed the rejection of claims 1 through 9 under 35 USC 103 as obvious on Pengilly [3] and Munro et al. (Munro) [4] "considered together." [5] Both Pengilly and Munro form PET by heating, in

either a batch or continuous process, a dicarboxylic acid with glycol, utilizing low ratios of glycol to acid (for example, 1.05:1.0 to 1.3:1.0 for Pengilly), and then polymerizing the low molecular weight ester formed therefrom in the presence of a catalyst. The processes differ in that the initial step of the Pengilly process is conducted at atmospheric pressure utilizing a preformed polyester solvent, whereas Munro operates at a higher pressure absent the solvent.

The appealed claims differ substantively from those of the parent application only in reciting "commercial scale production" utilizing "commercial scale quantities." Because the claims in the parent application had been rejected under 35 USC 103 on the same prior art and logic, the board merely adopted the previous board opinion, which held that the references established a case of "prima facie obviousness." The earlier board, agreeing with the examiner that Pengilly and Munro considered together rendered the claimed subject matter prima facie obvious because each suggested consonant advantages, stated:

> For example, Pengilly suggests that by using a polyester solvent shorter heating times and less glycol is required, and Munro et al suggests that by using higher pressures a shorter reaction time is required. One of ordinary skill in the polymer art would therefore expect that if higher pressures were used in other art processes (i.e., Pengilly) shorter reaction times would be necessary. [6]

The board considered the rebuttal evidence, a single affidavit by the inventor, Rinehart, to be insufficient. The primary apparent purpose of that evidence was to show the commercial inoperability of Pengilly and Munro, taken individually, compared to Rinehart's commercially used method. Rinehart's extensive affidavit included, however, substantial analysis of the entire field of polyester production and of what, in his view, Pengilly and Munro would actually teach those skilled in the art. The experimental pilot plant evidence is summarized below for a low charge molar ratio of glycol to acid (1.1:1.0):

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Table set at this point is not available. See table in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

Table set at this point is not available. See table in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

a1 The temperature was increased at a rate of 3° C/30 minutes from about 220°C to 245°C.

Rinehart alleged commercial success, based on the 1970 conversion by Goodyear Tire and Rubber Company (the assignee of Rinehart) from the ester interchange method, used since 1959, to Rinehart's direct esterification method.

The affidavit states:

> Both the Pengilly, and Munro and Maclean, procedures based on my experience and as evidenced from their patents are operable on a small scale. However, neither of their patents points to any recognition of the problems which arise from scaling up to a commercial process. It is implicit in their patents that the described procedures are satisfactory for commercial operation; but I have found that their techniques are not satisfactory on a commercial scale at about equimolar proportions. The advantages claimed by Munro and Maclean for their process are a short reaction time, improved color, higher softening point and a minimum ether content.

> However, I have found that as the Munro and Maclean process is scaled up beyond laboratory equipment the reaction becomes inconveniently long, the color deteriorates, the melting point is lowered and the ether content increases. The process of Pengilly was similarly operable on a small scale and not suitable for scale-up to a commercial process.

The board concluded that the affidavit evidence did not rebut its finding of prima facie obviousness because, in its view, the prior art clearly suggested higher pressure, together with an expected attendant advantage of increased reaction rate, as a solution to the commercial difficulties allegedly encountered by Rinehart. Moreover, the recitation to which the affidavit is directed, "commercial scale production" utilizing "commercial scale quantities," was viewed as "inherently" obvious. The board did not consider the utilization of the claimed method by Rinehart's assignee to be evidence of commercial success sufficient to establish unobviousness.

Issue

Whether, in the light of all the evidence, the claimed method would have been obvious at the time the invention was made.

Opinion

[2] Pengilly and Munro individually teach methods for the production of PET which differ, in different respects, from that claimed by Rinehart. A determination under 35 USC 103, however, requires consideration of the entirety of the disclosure

made by the two references to those skilled in the art.

[3] A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. Once such a case is established, it is incumbent upon appellant to go forward with objective evidence of unobviousness. In re Fielder, 471 F.2d 640, 176 USPQ 300 (CCPA 1973).

Prima Facie Obviousness

On the appeal involving Rinehart's parent application, the board was limited to the sterile evaluation of the claims and the prior art necessitated by availability of only the application and the cited references. Based on that evaluation, that board stated:

> We agree with the examiner that, in view of Munro et al., it would be obvious to operate the process of Pengilly at superatmospheric pressure. Looking at it from another point of view, it would be obvious in view of Pengilly to employ preformed ester as a solvent in the reaction of Munro et al.

On the appeal of the present application, the board stated:

> With regard to the rejection under Section 103, we find ourselves in substantial agreement with the position of the examiner as set forth in his answer. The claims on appeal are in essence the same as those in Serial No. 667,854, which is now before the District Court for the District of Columbia (Civil Action 666-71), the basic difference being the involved claims recite and are limited to "commercial scale production" utilizing "commercial scale quantities." The claimed invention is otherwise identical insofar as the material limitations defined are concerned. The claims in parent case Serial No. 667,854 were rejected under Section 103 over the same art

applied herein and essentially for the same reasons. Insofar as the question of whether or not the combination of the teachings of Pengilly and Munro et al would render the claimed process prima facie obvious, the same arguments were presented by appellant and the examiner in both the prior case and herein. Based on these arguments, the Board of Appeals agreed with the position of the examiner and affirmed the rejection. Appellant has set forth no good and sufficient reason why we should reconsider the prior Board decision or reach any other conclusion based on the arguments alone; we therefore adhere to that position and adopt it as our own.

The only remaining question for this Board to consider with regard to the Section 103 rejection is whether or not the affidavit filed under the provisions of Rule 132 is sufficient to rebut the prima facie case: in our opinion, it is not.

[4] The board erred in adopting the earlier opinion. The basis for evaluation and for decision had changed. The present board had before it not only the application and the prior art but all of the unrebutted facts established in Rinehart's affidavit. At that stage no question of prima facie obviousness remains. The appealed claims must be reconsidered in the light of all the evidence, and the resultant finding, that the claimed invention would or would not have been obvious, is to be made in such light.

[5] The concept of rebuttable prima facie obviousness is well established. Cf. In re Freeman, 474 F.2d 1318, 177 USPQ 139 (CCPA 1973); In re Klosak, 59 CCPA 862, 455 F.2d 1077, 173 USPQ 14 (1972); In re D'Ancicco, 58 CCPA 1057, 439 F.2d 1244, 169 USPQ 303 (1971). It is not, however, a segmented concept. When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. Though the burden of going forward to rebut the prima facie case remains with the applicant, the question of whether that burden has been successfully carried requires that the entire path to decision be retraced. An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself. Though the tribunal must begin anew, a final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached by an earlier board upon a different record.

[6] The board's analytical process appears to have resulted, at least in part, from Rinehart's erroneous argument that the mere inclusion of "commercial scale production" and "commercial scale quantities" served to patentably distinguish the appealed claims over those in the parent application. In response, the board engaged in comparison of the two sets of claims and

emphasized their essential identity. Whether engendered by Rinehart's arguments, the concentration on the "inherent obviousness" of scaling up led Rinehart and the solicitor into error.

[7] Rinehart erred in contending that the mere insertion into the claims of "commercial scale," without more, would constitute a distinguishing limitation. Though inclusion of the phrase in the claims does no harm, it is clear that mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled. Moreover, absent evidence to the contrary, nothing in Pengilly or Munro indicates that their processes are not effective on a commercial scale, and Rinehart concedes that commercial operation is implicit in the reference patents.

Rinehart argues here that merely because the appealed claims include a "crucial limitation" to

commercial quantities, they were "different claims" and that the board could not therefore have applied the earlier decision to them. We cannot agree. Absent the evidence in Rinehart's affidavit, use of commercial quantities in the processes of the references would have been obvious. If all Rinehart had done was to add the broad "commercial scale" phrases, the board's treatment would have been correct. It could not have found that the mere use of commercial quantities established unobviousness of the invention as a whole. But Rinehart did more. He submitted substantial evidence touching the basic question of whether his claimed process would have been obvious.

The board erred, as above indicated, in comparing the appealed claims to the earlier claims as though it had been established that the latter did in fact set forth an old or obvious process. In such comparison, the board proceeded as though the earlier claims were a kind of prior art to Rinehart and as though the earlier decision on those claims was a kind of res judicata. The differences between the two sets of claims were simply not at issue in this case. The sole question is whether Rinehart's claimed process would have been obvious in view of all the evidence.

The Evidence

The opinion of the board on the appeal involving the parent application included the following:

> Appellant alleges the existence of numerous difficulties with the processes of Pengilly and Munro et al. which, he claims, are overcome by combining the features of both processes. However, appellant's allegations are not supported by any evidence.

[8] The evidence now of record, in our view, does support Rinehart's allegations. The assertion that the processes of Pengilly and Munro cannot satisfactorily be scaled up is neither challenged nor rebutted. Though mere reference to "commercial scale quantities" in the claims and affidavit does not itself establish patentability, it does establish the environment of the invention. It outlines the problem solved and gives dimension to Rinehart's contribution. The claims must therefore be considered, and the references must be evaluated, in the light of an effort to achieve commercially effective production. As will appear hereinbelow, the affidavit evidence also spotlights portions of the prior art disclosures indicating unobviousness of the claimed process.

It is true that Pengilly and Munro both disclose processes for polyester production by direct esterification. Rinehart's affidavit admits that he began with an effort to employ the process of Pengilly on a commercial scale and that the only essential difference between the claimed process and that of Pengilly is the employment of superatmospheric pressure.

The board adopted the earlier opinion, which considered the claimed process as either that of Pengilly with the substitution of the superatmospheric pressure disclosed by Munro or that of Munro with the use of a preformed polyester as disclosed by Pengilly. But that view of the claimed process does not end the inquiry. The question remains whether it would have been obvious, in scaling up Pengilly's process, to have employed Munro's higher pressures or in scaling up that of Munro to have employed Pengilly's preformed polyester.

[9] The tribunals below did not meet the requirement of establishing some predictability of success in any attempt to combine elements of the reference processes in a commercial scale operation. As in In re Naylor, 54 CCPA 902, 369 F.2d 765, 152 USPQ 106 (1966), we find nothing in the record which would lead one of ordinary skill to anticipate successful production on a commercial scale from a combination of such elements, without increase in glycol-acid ratio. The record in fact reflects the contrary. The view that success would have been "inherent" cannot, in this case, substitute for a showing of reasonable expectation of success. Inherency and obviousness are entirely different concepts. In re Spormann, 53 CCPA 1375, 363 F.2d 444, 150 USPQ 449 (1966); In re Adams, 53 CCPA 996, 356 F.2d 998, 148

USPQ 742 (1966).

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The board cited the indication in both Pengilly and Munro that their processes led to rapid reaction time and concluded that improved reaction time would be expected if elements of those processes were combined. The evidence of record establishes, however, that reaction times of both prior processes lengthen as the processes are scaled up.

The board held the view that Munro's teaching of higher pressures to increase reaction rate would have provided an obvious solution to the problem Rinehart encountered in scaling up the process of Pengilly. But Rinehart's problem was not the need for increased reaction rate. It was, as the evidence established, the existence of lumps of frozen polymer. That problem is nowhere alluded to in either Pengilly or Munro, and of course no suggestion of a solution appears in either reference.

Moreover, Pengilly suggested that superatmospheric pressure was productive of certain disadvantages, particularly the need for use of a "large excess" of glycol. The use of superatmospheric pressure in a direct esterification process was referred to in other prior patents of record. With the exception of Munro, however, each such reference cited disadvantages of its use or an inability to find it workable. Munro's disclosure of superatmospheric pressure is rendered an abstraction with respect to appellant's problem by Munro's indication of the same excess glycol requirement when a large scale operation is contemplated. Munro employs a large excess of glycol (a ratio of glycol to acid of 3:1) in his example 5, the only example devoted to larger scale production. Rinehart's large scale production process is limited to a substantially equimolar ratio of glycol to acid. In view of all of the evidence, we cannot agree that Munro would suggest to one skilled in the art the use of superatmospheric pressure to solve the problem of scaling up the process of Pengilly.

Similarly, we find no suggestion in Pengilly or in Munro that Pengilly's preformed ester be employed in Munro's process to overcome the problems encountered in scaling up the process of Munro. Munro, as co-inventor with Lewis in earlier British Patent No. 776,282, was familiar with the use of a preformed polyester in direct esterification, yet neither Munro nor his co-inventor Maclean suggested its use with superatmospheric pressure in the cited reference. We find that the Munro patent contains its own solution to large scale operation, i.e., the use of excess glycol referred to above. That solution is not employed by appellant.

[10] Absence of any suggestion in either Pengilly or Munro that features of the process of one should be combined with features of the other to achieve the commercial scale production of which neither is capable requires a holding that the rejection herein was improper. In re Avery, 518 F.2d 1228, 186 USPQ 161 (CCPA 1975). In view of that holding, it is unnecessary to consider Rinehart's allegations of commercial success and satisfaction of long-felt need.

The decision of the board is reversed.

Footnotes

Footnote 1. The present application is a continuation-in-part of application serial No. 667,854 (parent), filed September 14, 1967, which in turn is a continuation-in-part of application serial No. 254,754, filed January 29, 1963, both of which are now abandoned. Prior to the present appeal, the rejection of parent application was appealed to the U.S. District Court for the District of Columbia. Goodyear Tire & Rubber Co. v. Schuyler, Com'r., Civil No. 666-71 (D.D.C., Feb. 25, 1975). Upon stipulation, that action was dismissed with prejudice, after the express abandonment of the parent application, but without

prejudice to the allowance of materially different claims, or of the same or similar claims on a record supporting them, such as the record now before us.

Footnote 2. The solvent may include stabilizer, catalyst, and ether

Footnote 3. U.S. Patent No. 3,427,287 issued February 11,

Footnote 4. U.S. Patent No. 3,050,533 issued August 21, 1962.

Footnote 5. The board also affirmed a double patenting rejection of those claims under 35 USC 101 based upon the copending parent application. Express abandonment of the parent application, subsequent to the board's decision, moots the issue.

Footnote 6. The earlier board also speculated that Munro's continuous process may "actually involve the use of preformed ester as the reaction solvent if the reaction takes place throughout the reactor and if, during the initial part of the process, the product is not withdrawn as rapidly as it is formed."

- End of Case -

FULL TEXT OF CASES (USPQ2D)
All Other Cases
Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016 (3/5/1991)

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.

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Decided March 5, 1991
Nos. 90-1273, -1275

Headnotes

PATENTS

1. Patentability/Validity - Date of invention - Conception (§ 115.0403)

Conception of chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property; thus, when inventor of gene, which is chemical compound albeit complex one, is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until reduction to practice has occurred, and until after gene has been isolated.

2. Patentability/Validity - Date of invention - Conception (§ 115.0403)

Conception of generalized approach for screening DNA library that might be used to identify and clone erythropoietin gene of then-unknown constitution is not conception of "purified and isolated DNA sequence" encoding human EPA, since it is not "definite and permanent idea of the complete and operative invention."

3. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Federal district court did not err in holding non-obvious claims for purified and isolated DNA sequence encoding human hormone erythropoietin, in view of evidence showing that procedures may have been

obvious to try, but also showing that there was no reasonable expectation of success.

4. Patentability/Validity - Specification - Best mode (§ 115.1107)

Determination of whether best mode requirement is satisfied is question of fact and thus is reviewed under clearly erroneous standard.

5. Patentability/Validity - Specification - Best mode (§ 115.1107)

Biological deposit is required to satisfy best mode requirement, for patents involving novel, genetically-engineered biological subject matter, if invention is incapable of being practiced without access to that organism, but if organism is created by insertion of genetic material into cell obtained from generally available sources, then cell deposit itself is not necessary and all that is required is description of best mode and adequate description of means of carrying out invention; if cells can be prepared without undue experimentation from known materials, based on description in patent specification, deposit is not required.

6. Patentability/Validity - Specification - Best mode (§ 115.1107)

Evidence showing that scientists were unable to duplicate inventor's genetically-heterogeneous best mode cell strain does not demonstrate that best mode requirement is not satisfied, since issue is whether disclosure is "adequate," and exact duplication is not necessary.

7. Patentability/Validity - Specification - Enablement (§ 115.1105)

Issue of whether claimed invention is enabled under 35 USC 112 is question of law that is reviewed de novo.

8. Patentability/Validity - Specification - Enablement (§ 115.1105)

Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for DNA sequences encoding which has claimed every possible analog of gene containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims, since, in view of structural complexity of EPO gene, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

9. Infringement - Defenses - Fraud or unclean hands (§ 120.1111)

Ultimate conclusion of inequitable conduct is reviewed under abuse of discretion standard, but underlying factual findings are reviewed under clearly erroneous standard.

10. Patentability/Validity - Specification - Enablement (§ 115.1105)

Federal district court erred by concluding that patent for method for purification of erythropoietin sufficiently enabled person of ordinary skill in art to obtain homogeneous EPO from natural sources having mean in vivo specific activity of at least 160,000, since court erred in accepting in vitro data as

support for claims containing in vivo limitation.

11. Patentability/Validity - Specification - Claim adequacy (§ 115.1109)

Patent construction - Claims - Defining terms (§ 125.1305)

Claim whose meaning is in doubt is properly declared invalid, especially when there is close prior art; thus, federal district court did not err in holding that claim for homogeneous erythropoietin which has specific activity limitation of "at least about" 160,000 was indefinite, although such holding does not preclude any and all uses of term "about" in patent claims, since such term may be acceptable in appropriate fact situations.

Particular patents - Chemical - Erythropoietin

4,677,195, Hewick and Seehre, method for the purification of erythropoietin and erythropoietin compositions, claims 1, 3, 4, and 6 invalid.
4,703,008, Lin, DNA sequences encoding erythropoietin, claims 2, 4, and 6 valid and infringed; claims 7, 8, 23-27, and 29 invalid.

Case History and Disposition:

Appeal from the U.S. District Court for the District of Massachusetts, Young, J. (Saris, U.S. magistrate); 13 USPQ2d 1737 .

Action by Amgen Inc. against Chugai Pharmaceutical Co. Ltd. and Genetics Institute Inc. for infringement of patent no. 4,703,008, to which defendants counterclaimed alleging infringement of patent no. 4,677,195. From federal district court decision holding certain claims of both patents valid and infringed, and holding other claims invalid, parties cross-appeal. Affirmed in part, reversed in part, and vacated in part.

Attorneys:
Edward M. O'Toole, Michael F. Borun, Richard A. Schnurr, and Christine A. Dudzik, of Marshall, O'Toole, Gerstein, Murray & Bicknell, Chicago, Ill.; Steven M. Odre and Robert D. Weist, Thousand Oaks, Calif., for Amgen.

Kurt E. Richter, Eugene Moroz, William S. Feiler, and Michael P. Dougherty, of Morgan & Finnegan, New York, N.Y., for Chugai Pharmaceutical.

William F. Lee, William McElwain, Ian Crawford, David Marder, David B. Bassett, and Sarianna T. Honkola, of Hale & Dorr, Boston, Mass., for Genetics Institute.

Judge:
Before Markey, Lourie, and Clevenger, circuit judges.

Opinion Text

Opinion By:
Lourie, J.

This appeal and cross appeal are from the March 4, 1990, judgment of the United States District Court for the District of Massachusetts, No. 87-2617-Y, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 13 USPQ2d 1737 (1990), and involve issues of patent validity, infringement, and inequitable conduct with respect to two patents: U.S. Patent, 4,703,008 ('008), owned by Kirin-Amgen Inc. (Amgen), and U.S. Patent 4,677,195 ('195), owned by Genetics Institute, Inc. (GI).
Chugai Pharmaceutical Co., Ltd. (Chugai) and Genetics Institute, Inc. (collectively defendants) assert on appeal that the district court erred in holding that: 1) Amgen's '008 patent is not invalid under 35 U.S.C. §§102(g) and 103; 2) the '008 patent is enforceable; 3) the failure of Amgen to deposit the best mode host cells was not a violation of the best mode requirement under 35 U.S.C. §112; and 4) claims 4 and 6 of GI's '195 patent are invalid for indefiniteness under 35 U.S.C. §112.
On cross appeal, Amgen challenges the district court's holdings that: 1) claims 1 and 3 of the '195 patent are enabled; 2) the '195 patent is enforceable; 3) this is not an exceptional case warranting an award of attorney fees to Amgen; and 4) claims 7, 8, 23-27 and 29 of the '008 patent are not enabled by the specification.
We affirm the district court's holdings in all respects, except that we reverse the court's ruling that claims 1 and 3 of the '195 patent are enabled. We also vacate that part of the district court's judgment relating to infringement of those claims.

BACKGROUND 1

Erythropoietin (EPO) is a protein consisting of 165 amino acids which stimulates the production of red blood cells. It is therefore a useful therapeutic agent in the treatment of anemias or blood disorders characterized by low or defective bone marrow production of red blood cells.
The preparation of EPO products generally has been accomplished through the concentration and purification of urine from both healthy individuals and those exhibiting high EPO levels. A new technique for producing EPO is recombinant DNA technology in which EPO is produced from cell cultures into which genetically-engineered vectors containing the EPO gene have been introduced. The production of EPO by recombinant technology involves expressing an EPO gene through the same processes that occur in a natural cell.

THE PATENTS

On June 30, 1987, the United States Patent and Trademark Office (PTO) issued to Dr. Rodney Hewick U.S. Patent 4,677,195, entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions" (the '195 patent). The patent claims both homogeneous EPO and compositions thereof and a method for purifying human EPO using reverse phase high performance liquid chromatography. The method claims are not before us. The relevant claims of the '195 patent are:
1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement

as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.
3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective

amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.
4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.
6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically acceptable vehicle.
Dr. Hewick assigned the patent to GI.
The other patent in this litigation is U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the '008 patent), issued on October 27, 1987, to Dr. Fu-Kuen Lin, an employee of Amgen. The claims of the '008 patent cover purified and isolated DNA sequences encoding erythropoietin and host cells transformed or transfected with a DNA sequence. The relevant claims are as follows:
2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.
6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.
7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.
8. A cDNA sequence according to claim 7.
23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.
24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.
25. A transformed or transfected mammalian host cell according to claim 24.
26. A transformed or transfected COS cell according to claim 25.
27. A transformed or transfected CHO cell according to claim 25.
29. A procaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

PROCEDURAL HISTORY

On October 27, 1987, the same day that the '008 patent was issued, Amgen filed suit against Chugai and GI. It alleged that GI infringed the '008 patent by the production of recombinant EPO (rEPO) and by use of transformed mammalian host cells containing vectors with DNA coding for the production of human EPO, and that Chugai, as a result of a collaborative relationship with GI, had induced and/or contributed to the direct infringement of the '008 patent by GI. Amgen further sought a declaration that GI's '195 patent is invalid under 35 U.S.C. §§102, 103, and 112, or, in the alternative, that Amgen does not infringe the claims of the '195 patent, and a declaration that GI and Chugai's future activities in the production and sale of rEPO will infringe the '008 patent. 2
GI and Chugai answered and counterclaimed, asserting several affirmative defenses, including invalidity under 35 U.S.C. §§101, 102, 103, and 112; non-infringement; failure to make deposits at a public depository of biological materials allegedly necessary for enabling the best mode of practicing the invention; and unenforceability of the

patent because of Amgen's alleged inequitable conduct before the PTO. GI also counterclaimed, alleging that Amgen infringed the '195 patent, asserting unfair competition, and seeking a declaratory judgment that the '008 patent was invalid and not infringed.

GI and Chugai then filed a joint motion for a partial summary judgment that Amgen infringed the claims of the '195 patent. Chugai also filed its own motion for summary judgment. On February 24, 1988, the district court granted GI's and Chugai's motion for partial summary judgment and, on January 31, 1989, the court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim, an issue that is not now before us.

In response to Amgen's motion for a preliminary injunction, the district court, on February 7, 1989, issued an order finding that "Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and the attendant burdens on a new company; ..." and that, as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest finding, the court determined that it would not enter an order to delay or prevent production or shipping of EPO, but would require the defendant GI to place with the court all profits from the sale of EPO.

In order to expedite trial, the parties consented to trial before a magistrate. The judge entered judgment upon findings of fact and conclusions of law set forth by the magistrate. With respect to Amgen's '008 patent, the court held that claims 2, 4, and 6 are valid, enforceable and have been infringed by GI; that infringement was not willful; that claims 7, 8, 23-27, and 29 are invalid for lack of enablement under 35 U.S.C. §112 but, if valid, were infringed by GI; that the '008 patent does not contain a process claim; and that Chugai has not infringed, contributorily infringed, or induced infringement of any claim of the '008 patent. The court also dismissed Amgen's complaint against Chugai.

With respect to GI's '195 patent, the court concluded that claims 1 and 3 are valid, enforceable, and have been infringed by Amgen; that Amgen has not infringed claims 2 and 5; that Amgen's infringement was not willful; and that claims 4 and 6 are invalid for indefiniteness under 35 U.S.C. §112, but, if valid, were infringed by Amgen. The court also concluded that Amgen did not misuse the '008 patent and that this was not an "exceptional" case under 35 U.S.C. §285.

DISCUSSION

I. AMGEN's '008 PATENT (Lin)

A. *Alleged prior invention under 35 U.S.C. §102(g)*

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

A person is entitled to a patent unless-(g) before the applicant's invention thereof the invention was made ... by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Defendants assert error in the district court's legal conclusion that in this case Lin's conception occurred simultaneously with reduction to practice. *See e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1988), *cert. denied,* 480 U.S. 947 (1987). They claim that Fritsch was first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library, which was the strategy which the district court found eventually resulted in the successful identification and isolation of the EPO gene. Defendants further claim that Fritsch conceived this strategy in 1981, was diligent until he reduced the invention to practice in May of 1984, and thus should be held to be a 102(g) prior inventor over Lin, who reduced the invention to practice in September of 1983.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech,* 802 F.2d at 1376, 231 USPQ at 87 (citing 1 *Robinson on Patents* 532 (1890)); *Coleman v. Dines,* 754 F.2d 353, 359,

224 USPQ 857, 862 (Fed. Cir. 1985) (citing *Gunter v. Stream,* 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)). Conception requires both the idea of the inven

tion's structure and possession of an operative method of making it. *Oka v. Youssefyeh,* 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988).

In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment. This situation results in a simultaneous conception and reduction to practice. *See* 3 D. Chisum, *Patents* §10.04[5] (1990). We agree with the district court that that is what occurred in this case.

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin; Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

[1] A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka,* 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.,* encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.,* until after the gene has been isolated.

Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

[2] Defendants further argue that because the trial court found that the probing and screening method employed by Lin is what distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a definite and permanent idea of the complete and operative invention." Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. *See Coleman,* 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.

The record indicates that several companies, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:
Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.
13 USPQ2d at 1760. As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice

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had been achieved; Lin was first to accomplish that goal.
Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.

B. *Alleged obviousness of the inventions of claims 2, 4, and 6*

Claim 2, as noted above, recites a purified and isolated DNA sequence, and claims 4 and 6 are directed to host cells transformed with such a DNA sequence. The district court determined that claims 2, 4, and 6 are not invalid under 35 U.S.C. §103, concluding that the unique probing and screening method employed by Lin in isolating the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art. 3
Obviousness under Section 103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.,* 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied,* 481 U.S. 1052 (1987). The district court stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.,* 837 F.2d 469 473, 5 uSPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*
[3] The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." 4 13 USPQ2d at 1768. While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success. *See In re O'Farrell,* 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).
Defendants challenge the district court's determination, arguing that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony. One

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witness, Dr. Davies of Biogen, another biotechnology company that had worked on EPO, stated that he could not say whether Biogen scientists would have succeeded in isolating the EPO gene if Biogen had the EPO fragments that were available to Lin in 1983. Dr. Wall, a professor at UCLA, testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. He said, "you couldn't be certain where in the genomic DNA your probe might fall." The court found that no one had successfully screened a genomic library using fully-

degenerate probes of such high redundancy as the probes used by Lin. In the face of this and other evidence on both sides of the issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by Lin would have been obvious in September 1983. We are not persuaded that the court erred in its decision.

Defendants assert that whether or not it would have been obvious to isolate the human EPO gene from a gDNA library with fully-degenerate probes is immaterial because it was obvious to use the already known monkey EPO gene as a probe. Defendants point out that, in the early 1980s, Biogen did significant work with an EPO cDNA obtained from a baboon, and that they used it as a probe to hybridize with the corresponding gene in a human gDNA library. However, this technique did not succeed until after Lin isolated the EPO gene with his fully-degenerate set of probes.

To support its obviousness assertion, defendants rely upon the testimony of their expert, Dr. Flavell, who testified that the overall homology of baboon DNA and human DNA was "roughly 90 percent". While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time.

Indeed, the district court found that Lin was unsuccessful at probing a human gDNA library with monkey cDNA until after he had isolated the EPO gene by using the fully-degenerate probes. Based on the evidence in the record, the district court found there was no reasonable expectation of success in obtaining the EPO gene by the method that Lin eventually used. While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious. The district court thoroughly examined the evidence and the testimony. We see no error in its result. Moreover, if the DNA sequence was not obvious, host cells containing such sequence, as claimed in claims 4 and 6, could not have been obvious. We conclude that the district court did not err in holding that the claims of the patent are not invalid under Section 103.

C. *Best Mode*

Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. §112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.

The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims 5 and that a deposit of the preferred CHO cells was not necessary.

[4] A determination whether the best mode requirement is satisfied is a question of fact, *DeGeorge v. Bernier,* 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985); we

therefore review the district court's finding under a clearly erroneous standard.

35 U.S.C. §112 provides in relevant part: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, *and shall set forth the best mode contemplated by the inventor of*

carrying out his invention.
(Emphasis added).
This court has recently discussed the best mode requirement, pointing out that its analysis has two components. *Chemcast Corp. v. Arco Indus. Corp.,* 913 F.2d 923, 927, 16 USPQ2d 1033, 1036 (Fed. Cir. 1990). The first is a subjective one, asking whether, at the time the inventor filed his patent application, he contemplated a best mode of practicing his invention. If he did, the second inquiry is whether his disclosure is adequate to enable one skilled in the art to practice the best mode or, in other words, whether the best mode has been concealed from the public. The best mode requirement thus is intended to ensure that a patent applicant plays "fair and square" with the patent system. It is a requirement that the *quid pro quo* of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there must be no concealment of a mode known by the inventor to be better than that which is disclosed. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384-85, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). Section 282 imposes on those attempting to prove invalidity the burden of proof. We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.
As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was disclosed because both were disclosed. 6
Defendants argue that this disclosure is not enough, that a deposit of the cells was required. Defendants contend that "[i]n the field of living materials such as microorganisms and cell cultures," we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor. This presents us with a question of first impression concerning the best mode requirement for patents involving novel genetically-engineered biological subject matter.
For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention. This practice arose out of the development of antibiotics, when microorganisms obtained from soil samples uniquely synthesized antibiotics which could not be readily prepared chemically or otherwise. *In re Argoudelis,* 434 F.2d 1390, 168 USPQ 99 (CCPA 1970). Such a deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. §112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required. *See, e.g., In re Wands,* 858 F.2d 731, 735-36, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988) ("Where an invention depends on the use of living materials ... it may be impossible to enable the public to make the invention (*i.e.,* to obtain these living materials) solely by means of written disclosure."); *In re Lundak,* 773 F.2d 1216, 1220, 227 USPQ 90, 93 (Fed. Cir. 1985) ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *see generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement,* 67 J. Pat. & Trademark Off. Soc'y 569, 607 (1985) ("The deposit requirement is a non-statutory mechanism for ensuring compliance with the 'enabling' provision under 35 U.S.C. §112.").
The district court found that the claims at issue require the use of biological materials

that were capable of being prepared in the laboratory from readily available biological cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified that the isolation of the preferred strain was a "routine limited dilution cloning procedure[ ]" well known in the art. Dr. Simonsen, GI's

own expert, testified that the disclosed procedures were "standard" and that:
with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually reproduce-well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.
The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the *best mode* host cells, could be practiced by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.
[5] These materials are therefore not analogous to the biological cells obtained from unique soil samples. When a biological sample required for the practice of an invention is obtained from nature, the invention may be incapable of being practiced without access to that organism. Hence the deposit is required in that case. On the other hand, when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. *See Feldman v. Aunstrup,* 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public."), *cert. denied,* 424 U.S. 912 [188 USPQ 720] (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the *best mode* of preparing the cells has been disclosed and the best mode cells have been enabled, *i.e.,* they can be prepared by one skilled in the art from known materials using the description in the specification.
Defendants also contend that the examiner's rejection of the application that matured into the '008 patent for failure to make a publicly accessible biological deposit supports its argument. U.S. Patent Application Serial No. 675,298, Prosecution History at 179 (First Rejection July 3, 1986). However, that rejection was withdrawn after an oral interview and a written argument that the invention did not require a deposit. *Id.* at 208.
We also note that the PTO has recently prescribed guidelines concerning the deposit of biological materials. *See* 37 C.F.R. §1.802(b) (1990) (biological material need not be deposited "if it is known and readily available to the public or can be made or isolated without undue experimentation"). The PTO, in response to a question as to whether the deposit requirement is applicable to the best mode requirement, as distinct from enablement, said:
The best mode requirement is a safeguard against the possible selfish desire on the part of some people to obtain patent protection without making a full disclosure. The requirement does not permit an inventor to disclose only what is known to be the second-best embodiment, retaining the best .... The fundamental issue that should be addressed is whether there was evidence to show the quality of an applicant's best mode disclosure is so poor as to effectively result in concealment. *In re Sherwood,* 615 F.2d 809, 204 USPQ 537 (CCPA 1980). If a deposit is the only way to comply with the best mode requirement then the deposit must be made.
52 *Fed.Reg.* 34080, 34086 (Sept. 8, 1987). 7
We see no inconsistency between the district court's decision, which we affirm here, and these guidelines.
[6] Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate," not that an exact duplication is necessary. Indeed, the district court stated that
he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian

host cell strains or lines with similar levels of production identified in Example 10.
13 USPQ2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible. *See In re Gay,* 309 F.2d 769, 773, 135 USPQ 311, 316 (CCPA 1962).
Defendants finally argue that Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment. We have already stated that deposit of the host cells containing the rEPO gene was not necessary to satisfy the best mode requirement of Section 112. The best mode was disclosed and a deposit was not necessary to carry it out. Therefore, the fact that some cells were deposited, but not others, is irrelevant.

D. *Enablement of claims 7, 8, 23-27, and 29*

Amgen argues that the district court's holding that GI "provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation" constituted legal error. 13 USPQ2d at 1776. Amgen specifically argues that the district court erred because it "did not properly address the factors which this court has held must be considered in determining lack of enablement based on assertion of undue experimentation," citing this court's decision in *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404.
Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. As claims 8, 23-27, and 29, dependent on claim 7, are not separately argued, and are of similar scope, they stand or fall with claim 7. *See In re Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1900 (Fed. Cir. 1990) (in banc).
[7] Whether a claimed invention is enabled under 35 U.S.C. §112 is a question of law, which we review *de novo. Moleculon Research Corp. v. CBS, Inc.,* 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied,* 479 U.S. 1030 (1987). "To be enabling under §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." *Atlas Powder Co. v. E.I. duPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).
That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *Id.* The essential question here is whether the scope of enablement of claim 7 is as broad as the scope of the claim. *See generally In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970); 2 D. Chisum, *Patents* §7.03[7][b] (1990).
The specification of the '008 patent provides that:
one may readily design and manufacture genes coding for microbial expression of polypeptides having primary conformations which differ from that herein specified for mature EPO in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions). DNA sequences provided by the present invention are thus seen to comprehend all DNA sequences suitable for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin, and selected from among: (a) the DNA sequences set out in FIGS. 5 and 6; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).
The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous.
In a deposition, Dr. Elliott, who was head of Amgen's EPO analog program, testified that he did not know whether the fifty to eighty EPO analogs Amgen had made "had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase

hemoglobin synthesis or iron uptake." Based on this evidence, the trial court concluded that "defendants had provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation." 13 USPQ at 1776. In making this determina

tion, the court relied in particular on the lack of predictability in the art, as demonstrated by the testimony of both Dr. Goldwasser, another scientist who worked on procedures for purifying urinary EPO (uEPO), and Dr. Elliott. After five years of experimentation, the court noted, "Amgen is still unable to specify which analogs have the biological properties set forth in claim 7." *Id.*

We believe the trial court arrived at the correct decision, although for the wrong reason. By focusing on the biological properties of the EPO analogs, it failed to consider the enablement of the DNA sequence analogs, which are the subject of claim 7. Moreover, it is not necessary that a patent applicant test all the embodiments of his invention, *In re Angstadt,* 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

[8] It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See Utter v. Hiraga,* 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); *In re Robins,* 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-Type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them.

In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

The district court properly relied upon *Fisher* 8 in making its decision. In that case, an applicant was attempting to claim an adrenocorticotrophic hormone preparation containing a polypeptide having at least twenty-four amino acids of a specified sequence. Only a thirty-nine amino acid product was disclosed. The court found that applicant could not obtain claims that are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. §112. It stated:

Appellant's parent application, therefore, discloses no products, inherently or expressly, containing other than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having at least 24 amino acids in the chain in the recited sequence. The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation. As for appellant's conclusion that the 25th to 39th acids in the chain are

unnecessary, it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids; it is quite another thing when they are not able to do so. In the latter situation, the statement is in no way "enabling" and hence lends no further support for the broad claim. We conclude that appellant's parent applica

tion is insufficient to support a claim as broad as claim 4.
requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.
Fisher, 427 F.2d at 836, 839, 166 USPQ at 21-2224.
Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.

E. *Inequitable Conduct*

Defendants argue that the '008 patent claims are unenforceable as a result of an asserted misrepresentation of the number of probes Lin used for the monkey gene cloning described in Example 3 of his patent. Relying on the district court's finding that Lin had said that a "full set" mixture of 128 "EpV" probes 9 was used for monkey cDNA screening, whereas only a 16-member "subset" of the EpV mixture was actually used, defendants argue that the court ought to have found that the representations were material.
[9] The essential elements of proof of inequitable conduct include intent to deceive and materiality. After finding threshold levels of materiality and intent, the trial court must balance the two and determine, in its discretion, whether inequitable conduct has occurred. *J.P. Stevens & Co. v. Lex Tex Ltd., Inc.,* 747 F.2d 1553, 1560, 223 USPQ 1089, 1092 (Fed. Cir. 1984), *cert. denied,* 474 U.S. 822 (1985). While we review an ultimate conclusion of inequitable conduct under an abuse of discretion standard, *Kingsdown Medical Consultants, Ltd. v. Hollister Inc.,* 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988) (in banc), *cert. denied,* 490 U.S. 1067 (1989), the underlying factual threshold findings are reviewed under a clearly erroneous standard.
Lin set out to clone the EPO gene by more than one method, including using degenerate human probes and monkey probes. It is not disputed that he did isolate the human EPO gene from a genomic library using two different 128-member pools of probes made from fragments of the human EPO protein. Thereafter, he also attempted to use the human sequence probes to find the monkey EPO cDNA to be used later as a probe to hybridize with the human EPO gene. Example 3 of the '008 patent describes this work, indicating that the screening yielded seven positive clones. It also reports that a subset of the human EpV mixture was used for DNA sequencing work. When Lin published his monkey cDNA cloning work in a scientific journal, he also reported the use of 128 EpV probes to screen the monkey library. Lin screened the monkey library with the full mixture of 128 EpV probes and with one of eight subsets of probes which made up the full EpV mixture. In response to a question whether a subset of EpV probes was used in the first screening of the monkey cDNA library, Lin testified:
I don't know which we used, the subset first or used the full set first. I cannot recall exactly. It looks like the subset was first defining the number, yes.
This answer constituted the sole basis for the court's finding that, "[a]t trial, Lin admitted he only used a subset of the EpV 128 probes in screening the cDNA library." 13 USPQ2d at 1778.
We consider that the district court's finding of an "admission" of misrepresentation in Lin's testimony

and its conclusion that GI "presented clear and convincing evidence of a misrepresentation" was clearly erroneous. That Lin did not recall whether he first screened the monkey cDNA library with a full set of probes or a subset of probes, and his answer that "it looks like" he used the subset, are certainly not clear admissions that he only used a subset. However, the district court was correct in concluding that, even if there had been an erroneous statement, it was not material because Lin succeeded in cloning the EPO gene first with his use of the fully-degenerate probes. Thus, his testimony does not provide clear and convincing evidence that he misrepresented to the PTO the number of probes used. He did use 128-member probes as well as a subset. Moreover, this evidence does not create an inference of an intent to mislead. The court

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properly concluded that there was no inequitable conduct in prosecuting the '008 patent.

II. GI's '195 PATENT (Hewick)

A. *Enablement of claims 1 and 3*

Amgen challenges the district court's determination that "the '195 patent enables a person of ordinary skill in the art to obtain homogeneous EPO [including rEPO and uEPO] from natural sources" having a mean *in vivo* specific activity of at least 160,000. 10 13 USPQ2d at 1794. Claims 1 and 3 contain the limitation that EPO have a specific activity of at least 160,000 IU/AU. The district court found, based upon expert testimony from both sides, that to those skilled in the art, in the absence of an express statement in the patent, the claims would be construed to refer to *in vivo* rather than *in vitro* specific activity. To support its challenge, Amgen asserts that the district court's determination is contradicted by GI's own bioassay data and by the district court's finding that "the '195 patent fails to enable the purification of rEPO." Amgen also asserts that the district court erred in relying solely on an *in vitro* measure of specific activity, having initially construed the '195 claims as requiring an *in vivo* measure to avoid invalidity for indefiniteness.

35 U.S.C. §112 requires that an invention be described "in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same." We review a determination of enablement as a question of law. *Moleculon Research Corp. v. CBS, Inc.,* 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied,* 479 U.S. 1030 (1987).

We do not consider the court's finding that the assay measurement was an *in vivo* one to be erroneous in view of the testimony it heard. That being the case, the question is whether the court erred in concluding that the claims requiring 160,000 IU/AU by an *in vivo* measurement were enabled. We conclude that it did err.

Defendants have produced no evidence that it ever prepared EPO with a specific activity of at least 160,000 IU/AU *in vivo* using the disclosed methods. In its report to the FDA, GI stated that it had purified uEPO material "to homogeneity" by subjecting partially purified uEPO material to reverse phase high performance liquid chromatography (RP-HPLC), the technique taught by Hewick in the '195 patent. The district court found that GI reported to the FDA that the specific activity of uEPO, based on *in vivo* bioassays, was only 109,000 IU/AU. 11 GI originally arrived at the figure of 160,000 IU/AU by calculation, before it had the capacity to derive quantitative information from bioassays. Hewick subjected the EPO to RP-HPLC, the EPO having an actual value of 83,000 IU/AU. After weighing the chromatograph, he found that "at least fifty percent" of the area under the chromatograph curve was attributable to something other than EPO. He then doubled the 83,000, and arrived at a theoretical specific activity of "at least about 160,000 IU/AU." That procedure, while possibly valid as a means for estimating the specific activity of a pure sample, does not establish that GI had a workable method for actually obtaining the pure material that it claimed.

Moreover, the work of others shows that Hewick did not enable the preparation of uEPO having an *in vivo* specific activity of at least 160,000, as the claims required. Dr. Kawakita, a scientist at Kummamoto University in Japan, reported an *in vivo* specific activity of 101,000 IU/AU when using

RP-HPLC according to Hewick's method. This is similar to the 109,000 value reported to the FDA by GI. Kawakita did report a value of 188,000, but did not follow the teachings in the '195 patent. Defendants also rely on the testimony of Fritsch that "I've also seen further data in Chugai's PLA indicating additional urinary EPO preparation that had activities of 190,000, I believe, units per absorbance unit." However, the document to which Fritsch referred was not offered into evidence by GI after Amgen objected to its introduction and is not before us.

Defendants argue that Dr. Kung's uEPO test result of 173,640 IU/AU in an *in vitro* test supports the enablement of its claims. Amgen argues that an *in vivo* test result would only have been 65 percent of the *in vitro* result and thus would not have met the 160,000 IU/AU limitation of the claims. The district court relied on Kung, despite the demonstrated disparity between the results of *in vitro* and *in vivo* testing.

[10] It is not absolutely clear to us that, for uEPO, the *in vivo* specific activity is 65 percent of the *in vitro* specific activity. Nonetheless, Kung's measurement, being *in vitro,* does not demonstrate enablement of the claimed invention, and that fact means that the court erred in finding enablement. Added to this fact is the difference that exists between the *in vivo* results for rEPO and uEPO 12 , and the other lack of support for the 160,000 limitation. Under these circumstances, we hold that the district court erred in accepting the *in vitro* data as support for claims containing what has been found to be an *in vivo* limitation.

In addition to the question of enablement regarding uEPO, the district court found that the only purification attempt on rEPO in the manner set out in the '195 patent failed to provide homogeneous EPO. The patent itself, in Example 2, discloses GI's purification efforts on rEPO and indicates that GI did not obtain purified rEPO. As the district court found, "[t]he patent does not contain any procedures ... for purifying rEPO to the point that RP-HPLC will be successful." 13 USPQ2d at 1758. Thus, the patent fails to enable purification of either rEPO or uEPO. 13 *See In re Rainer,* 377 F.2d 1006, 1012, 153 USPQ 802, 807 (CCPA 1967) ("specification is evidence of its own inadequacy").

The burden of showing non-enablement is Amgen's, not GI's, but in the case of a challenged patent, when substantial discovery has occurred, and there is no credible evidence that the claimed purified material can be made by those skilled in the art by the disclosed process, and all evidence from both the inventor and his assignee and from third parties is to the contrary, we conclude that Amgen has met its burden to show that the claims have not been adequately enabled. We do not hold that one must always prove that a disclosed process operates effectively to produce a claimed product. But, under these circumstances, we conclude that the court erred in holding that claims 1 and 3 were properly enabled.

B. *Indefiniteness of claims 4 and 6*

The district court held claims 4 and 6 of the '195 patent invalid because their specific activity limitation of "at least about 160,000" was indefinite. Defendants challenge this holding, asserting that there is no evidence that claims 4 and 6 do not comply with the requirements of 35 U.S.C. §112.

The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.,* 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits."). The district court found that "bioassays provide an imprecise form of measurement with a range of error" and that use of the term "about" 160,000 IU/AU, coupled with the range of error already inherent in the specific activity limitation, served neither to distinguish the invention over the close prior art (which described preparations of 120,000 IU/AU), nor to permit one to know what specific activity values below 160,000, if any, might constitute infringement. 13 USPQ2d at 1787. It found evidence of ambiguity in the fact

that Chugai, GI's partner, itself questioned whether the specific activity value of 138,000 IU/AU for its own rEPO was within the claim coverage.
In prosecuting the '195 patent, GI disclosed to the examiner a publication by Miyake et al., which discloses a uEPO product having an *in vivo* specific activity of 128,620 IU/AU. When the examiner noticed this disclosure late in the prosecution, he rejected the '195 claims with a specific activity limitation of "at least 120,000" as anticipated by the Miyake et al. disclosure. It was only after the "at least 120,000" claims were cancelled that GI submitted the "at least about 160,000" claim language. The court found the "addition of the word 'about' seems to constitute an effort to recapture ... a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and [the] 160,000 IU/AU" claims which were previously allowed. Because "the term 'about' 160,000 gives no hint as to which mean value between the Miyake et al. value of 128,620 and the mean specific activity level of 160,000 constitutes infringement," the court held the "at least about" claims to be invalid for indefiniteness. 13 USPQ2d at 1787-88. This holding was further supported by the fact that nothing in the specification, prosecution history, or prior art provides any

indication as to what range of specific activity is covered by the term "about," and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art. In his testimony, Fritsch tried to define "about" 160,000, but he could only say that while "somewhere between 155[,000] might fit within that number," he had not "given a lot of direct considerations to that...."
[11] When the meaning of claims is in doubt, especially when, as is the case here, there is close prior art, they are properly declared invalid. *Standard Oil Co. v. American Cyanamid Co.,* 774 F.2d 448, 453, 227 USPQ 293, 297 (Fed. Cir. 1985). We therefore affirm the district court's determination on this issue. We also note that, in view of our reversal of the district court's holding that claims 1 and 3 are valid, it is clear that claims 4 and 6 would also be invalid without the "about" limitation. In arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations, *e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) ("use of 'stretching ... at a rate exceeding about 10% per second' in the claims is not indefinite"), even though it is not here.

C. *Inequitable Conduct*

The district court concluded that GI did not engage in inequitable conduct with respect to the '195 patent. Amgen challenges this holding, asserting, *inter alia,* that GI displayed an intent to mislead by withholding data showing *in vivo* specific activity of homogenous uEPO and withholding information on the range of error in EPO bioassays.
It is fundamental that to establish inequitable conduct, an intent to deceive is required. *RCA Corp. v. Data General Corp.,* 887 F.2d 1056, 1065, 12 USPQ2d 1449, 1456-57 (Fed. Cir. 1989). A finding of an intent to deceive may follow from an assessment of materiality, knowledge, and surrounding circumstances, including evidence of good faith. *Kingsdown Medical Consultants Ltd. v. Hollister Inc.,* 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1067 (1989). The district court found no such intent, stating:
the record is devoid of any evidence that would establish deliberate knowing withholdings of any kind by Dr. Hewick or GI. Dr. Hewick was a credible witness who spoke carefully and candidly about his work ... There is no evidence that Dr. Hewick withheld any information he believed was material to the patent examiner.
Amgen, 13 USPQ2d at 1791. There is no clear error in this finding. Amgen raises no inequitable conduct issues that were not fully considered by the district court. We have reviewed the record and find no abuse of discretion on the part of the district court. This is also not an exceptional case.

III. OTHER ISSUES

In view of our conclusion that the district court erred as a matter of law in holding that claims 1 and 3 of the '195 patent are not invalid, we vacate the district court's holdings relating to infringement of those claims. We have considered the other arguments by counsel on both sides and find them to be without merit.

CONCLUSION

We conclude that the district court did not err in its findings that claims 2, 4, and 6 of the '008 patent are valid and enforceable and have been infringed by GI, and that claims 7, 8, 23-27, and 29 of the '008 patent are invalid; we therefore affirm the judgment of the court regarding the '008 patent. Because we conclude that claims 1, 3, 4, and 6 of the '195 patent are invalid, we affirm the judgment concerning claims 4 and 6 and reverse the judgment concerning claims 1 and 3.

COSTS

Each party shall bear its own costs.
AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART

Footnotes

Footnote 1. The district court, in a detailed opinion, fully sets out the scientific and historical background relating to the patents at issue. *See Amgen,* 13 USPQ2d at 1741-58. Familiarity with that opinion is presumed.

Footnote 2. Amgen subsequently filed a complaint with the United States International Trade Commission alleging that Chugai's importation of rEPO, manufactured in Japan using genetically engineered host cells, violated Section 337 of the Tariff Act of 1930 (19 U.S.C. §§1337, 1337a). The Commission entered an order terminating the investigation for lack of subject matter jurisdiction. This court vacated and remanded, holding that the Commission should have treated the complaint on the merits and not on jurisdictional grounds, and that the claims of Amgen's patent did not cover a process for producing rEPO. *Amgen, Inc. v. United States Int'l Trade Comm'n,* 902 F.2d 1532, 14 USPQ2d 1734 (Fed. Cir. 1990).

Footnote 3. We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.

Footnote 4. At this point, some explanation of the involved technology may be useful, consistent with that expressed in the district court opinion. DNA consists of two complementary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from one strand weakly bond to the bases of the opposite strand. A bonds with T, and G bonds with C to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule. The structure also includes 5-carbon sugar moieties with phosphate groups.

The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 (4x4x4) possible codons. Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a "redundancy" or "degeneracy" in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be

isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or a portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a "fully-degenerate" set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known.

Footnote 5. Defendants assert that all the claims should be invalid for failure to disclose the best mode. We perceive that the best mode issue only relates to the host cell claims, 4, 6, 23-27, and 29. Absent inequitable conduct, a best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with the best mode requirement. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940, 15 USPQ2d 1321, 1328 (Fed. Cir.), *cert. denied,* — U.S. —, 111 S.Ct. 296 (1990).

Footnote 6. In its opinion, the district court stated that "the best way to express EPO was from mammalian cells ... and that a cell line derived from 11 possible clones from the CHO B11, 3,.1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November 26, 1984." 13 USPQ2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells (the B11 3,.1 cell strain) and one micromolar-treated cells." *Id.*

Footnote 7. *See also* 53 *Fed. Reg.* 39420, 39425 (Oct. 6, 1989) (comment *re* "deposit [to] satisfy the best mode requirement"); 52 *Fed. Reg.* 34080, 34080 and 34084 (Sept. 8, 1987) (deposit may be required to satisfy enablement, best mode, or distinct claim requirements of §112).

Footnote 8. *Cf. Hormone Research Foundation, Inc. v. Genentech, Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990). In *Hormone Research,* this court, in a remand, directed the district court to consider the effect of *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 8 USPQ2d 1461 (Fed. Cir. 1989) and *In re Hogan,* 559 F.2d 595, 194 USPQ 527 (CCPA 1977) on *Fisher* in its enablement analysis. The facts of our case are distinguishable from those in *Hormone Research, United States Steel,* and *Hogan.*

Footnote 9. The probes designated "EpV" were from EPO amino acid sequence region 46-52.

Footnote 10. The potency of EPO in the '195 patent is stated as its specific activity, expressed as a ratio of International Units (which measures the ability of EPO to cause formation of red blood cells) per absorbance unit (the amount of light absorbed by a sample of EPO measured by a spectrophotometer at a given wavelength, 280 nanometers), *i.e.,* IU/AU.

Footnote 11. Defendants provided no evidence that faulty purification procedures or other missteps caused its failure to obtain 160,000 IU/AU *in vivo* material as claimed in the '195 patent.

Footnote 12. The court quoted Chugai to the effect that the *in vivo* activity of uEPO is 65 percent that of rEPO.

Footnote 13. Chugai's sample reported to the Food and Drug Administration was not purified by the disclosed process.

- End of Case -

FULL TEXT OF CASES (USPQ2D)
All Other Cases
In re O'Farrell (CA FC) 7 USPQ2d 1673 (8/10/1988)

In re O'Farrell (CA FC) 7 USPQ2d 1673

In re O'Farrell

U.S. Court of Appeals Federal Circuit
7 USPQ2d 1673

Decided August 10, 1988
No. 87-1486

Headnotes

PATENTS

1. Patentability/Validity -- Obviousness -- Evidence of (§ 115.0906)

Applicants' method of producing predetermined protein in stable form in host species of bacteria through genetic engineering is obvious within meaning of 35 USC 103 since reference, authored by two of three patent applicants and published more than one year prior to patent application date, contained detailed enabling methodology for practicing claimed invention, suggestion for modifying prior art to practice claimed invention, and evidence suggesting that invention could be successful, and reference thus rendered invention obvious to those of ordinary skill in art at time invention was made.

2. Patentability/Validity -- Obviousness -- Evidence of (§ 115.0906)

Experimenters' use of heterologous gene coded for ribosomal RNA, which is not ordinarily translated, rather than gene coded for predetermined protein, in plasmid cloning vector for introduction into host bacteria in genetic engineering experiment, does not require finding that applicant's claimed method of producing predetermined protein in host bacteria through genetic engineering was not obvious in view of published paper describing experiment, particularly observation that hybrid messenger RNA produced by experiment was apparently translated into protein, since it would have been obvious and reasonable to conclude from such observation that if gene coded for ribosomal RNA produced "junk" or "nonsense" protein, then use of gene coded for predetermined protein would result in production of "useful" protein, as application claims.

3. Patentability/Validity -- Obviousness -- In general (§ 115.0901)

Rejection of patent application cannot be overturned on ground that examiner and Board of Patent Appeals and Interferences applied impermissible "obvious to try" standard, since assignment of error for application of such standard usually occurs when invention is made by varying all parameters or trying each of numerous choices until successful without indication in prior art as to which parameters were critical or which choices were likely to be successful, or when invention is made by exploring promising new technology or general approach with only general guidance from prior art as to particular form of claimed invention or how to achieve it, and since neither situation is present in instant case.

4. Patentability/Validity -- Obviousness -- In general (§ 115.0901)

Finding of obviousness under 35 USC 103 requires only that prior art reveal reasonable expectation of success in producing claimed invention, rather than absolute prediction of such success.

Case History and Disposition:

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application, serial no. 180,424, filed by Patrick H. O'Farrell, Barry O. Polisky, and David H. Gelfand. From decision of Board of Patent Appeals and Interferences affirming final rejection of application on grounds of obviousness, applicants appeal. Affirmed.

Attorneys:
J. Bruce McCubbrey of Fitch, Even, Tabin & Flannery (Virginia H. Meyer, with them on brief), San Francisco, Calif., for appellant.

Harris A. Pitlick, associate solicitor, Patent and Trademark Office (Joseph F. Nakamura, solicitor and Fred E. McKelvey, deputy solicitor, with him on brief), for appellee.

Judge:
Before Markey, chief judge, and Rich and Nies, circuit judges.

Opinion Text

Opinion By:
Rich, J.

This appeal is from the decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (board) affirming the patent examiner's final rejection of patent application Serial No. 180,424, entitled "Method and Hybrid Vector for Regulating Translation of heterologous DNA in Bacteria." The application was rejected under 35 USC 103 on the ground that the claimed invention would have been obvious at the time the invention was made in view of a published paper by two of the three coinventors, and a publication by Bahl, Marians & Wu 1 *Gene* 81 (1976) (Bahl). We

affirm.
The claimed invention is from the developing new field of genetic engineering. A broad claim on appeal reads:

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Claim 1. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria comprising, providing a cloning vector which includes at least a substantial portion of a gene which is indigenous to the host species of bacteria and is functionally transcribed and translated in that species, said substantial portion of said indigenous gene further including the regulatory DNA sequences for RNA synthesis and protein synthesis but lacking the normal gene termination signal, and linking a natural or synthetic heterologous gene encoding said predetermined protein to said indigenous gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of said indigenous gene so that readthrough can occur from said indigenous gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.
Illustrative embodiments are defined in more specific claims. For example:
Claim 2. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria, comprising, providing an *E. coli* plasmid having an operator, a promoter, a site for the initiation of translation, and at least a substantial portion of the beta-galactosidase gene of the *E. coli* lactose opero